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OPINIONS IN ALLERGY

Influenza immunization in egg allergy: an update for the 2011–2012 season

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Summary

Flu vaccines contain detectable amounts of egg protein, which may pose a risk to egg-allergic individuals. The 2009 H1N1 influenza pandemic required mass vaccination in many countries, and the safety of flu immunization in egg allergy became of increasing public health importance. This article reviews recent literature and provides an updated guideline for immunization during the 2011–2012 flu season. Recent experience suggests that some vaccines with very low ovalbumin concentrations may be safe for use in primary care in carefully assessed low-risk individuals.

In 2009, we published guidelines for the safe administration of influenza vaccine in those allergic to egg [1]. We stratified risk of reaction based on severity of the previous allergic reaction to egg, the presence of coexistent asthma and the ovalbumin (OVA) content of the vaccines. Since the publication of our guidelines, there have been developments in our understanding of the safety of influenza vaccines in egg allergy. We have revaluated our guidance in the light of new information published in the last year and the UK Department of Health advice for influenza immunization for the 2011–2012 season [2].

Using our guidelines, a large Canadian case–control study has reported the safety of the AS03-adjuvanted pH1N1 vaccine (Arepanrix, GSK, Mississauga, ON, Canada) in egg allergy [3]. This study delivered vaccine with a maximum OVA content of 0.015 μg/mL. Of 830 egg-allergic children, there were no cases of anaphylaxis as an adverse event following immunization. Fifty percent of this group had a history of bronchial hyperreactivity, and 9% required a split two dose (10%, 90%) schedule for history of anaphylaxis to egg or uncontrolled asthma. Of the adverse events reported, there was one case of wheeze, possibly associated with anxiety, and two cases of generalized hives. Otherwise reactions were similar to control cases. No increased reactivity was observed in those who received the split dose, suggesting that they may have tolerated a single full-dose immunization [3]. Following this initial safety assessment, the Quebec flu immunization programme was rolled out to 3640 self-reported egg-allergic individuals, all immunized in physician supervised clinics. There were two cases requiring adrenaline, neither of whom in retrospect met criteria for anaphylaxis. In addition, there were, a further seven cases of cough, 17 throat symptoms and 69 mild allergic reactions [3].

Our 2009 guidelines considered the use of prior skin-testing redundant. This has been confirmed by further investigations [4]. Using a two dose-split schedule with seasonal vaccines (of unstated OVA content), they immunized 171 egg-allergic children. They compared vaccine safety over several seasons and found that prior skin testing did not predict reactions to vaccination. We continue not to recommend routine use of skin prick or intra-dermal testing prior to immunization in egg allergy. In the latter study, no one had a history of anaphylaxis to egg, but the majority had concomitant asthma. There were seven systemic reactions, but no

cases of anaphylaxis, the majority occurred within 30 min of the first 1/10th dose. This study shows that children with egg allergy and asthma should be considered at higher risk. We continue to support the use of step 3 of the British Thoracic Society/SIGN guidelines, where a long acting β2 agonist is added to inhaled corticosteroid therapy, as a higher risk cut-off in egg allergy [5]. Their results also indicate the need to know the OVA content of the vaccine.

Ovalbumin concentrations in flu vaccines

Ovalbumin concentrations in flu vaccines vary by season, manufacturer and batch [6–8]. Vaccinators must be aware of the OVA content of their currently available vaccines before use in egg allergy. Cell culture-based flu vaccines do not contain any egg protein residue, but may not always be available, as seen during the 2010 season in the United Kingdom. They may also be less efficacious than adjuvanted egg-based vaccines, especially in children [9]. A decision on vaccine use must be made on a balance of efficacy and safety. This will change depending upon the pathogenicity of the circulating flu strains, the OVA content of the vaccines and the susceptibility of the individual.

In Europe, the maximum OVA content of flu vaccines is up to 1 μg/dose [10]. As most flu vaccines use a 0.5 mL dose, then OVA concentration may be up to 2 μg/mL. This is higher than the 1.2 μg/mL concentration used in previous safety studies of flu vaccine in egg allergy [11]. Our current guidance is based on safety studies with vaccines containing much lower doses of OVA at 0.015 and 0.002 μg/mL [3, 12]. For the purposes of these guidelines, we have made an arbitrary cut-off below 10% of the historical 1.2 μg/mL safety limit: at <0.12 μg/mL, which we will refer to as *very low* OVA vaccines. Our cut-off is designed to show that more recent safety studies have *at least* an order of magnitude less OVA in their vaccines than previous studies. However, it should be noted that the safety of vaccines on either side of this guide concentration cannot be guaranteed. Vaccines with OVA between 0.12 μg/mL and the previous safety cut-off of 1.2 μg/mL are referred to as *low* egg vaccines. Vaccines with OVA content above 1.2 μg/mL, or where the OVA content of the vaccine is not stated, should not be used in egg allergy [3, 4].

Recommendations for seasonal flu vaccine in 2011–2012

In the coming season, there is no longer a requirement for immunization with pandemic H1N1 vaccine. The pH1N1 virus is still likely to be a dominant circulating strain and has been incorporated into the trivalent seasonal vaccine [2]. Our updated guidance is outlined in Table 1. Vaccination of low-risk individuals with *very low* OVA vaccine is safe in primary care. We have abandoned the use of split dose schedule for *very low* egg vaccines, as it appears to be as safe as single-dose immunization [3]. Split-dose immunization (0.05 mL followed by 0.45 mL 30 min later) should be used in higher risk individuals only if a *low* egg vaccine is to be used. Although some vaccination may be safe in primary care, general practitioners may require expert advice on risk stratification of their patients.

To summarize the updated guidance:

- An egg-free vaccine should be used if available.

Table 1. Revised criteria immunization of egg-allergic individuals in the absence of an egg-free vaccine

	Worst previous reaction to egg	*Very low* OVA vaccine protocol	*Low* OVA vaccine protocol
Lower risk	Previous mild gastrointestinal or dermatological reaction to egg AND positive diagnostics OR Positive diagnostics but never knowingly exposed to egg	Single-dose schedule 0.5 mL intramuscular dose of a *very low* egg content vaccine if egg-free vaccine not available in primary care with a 60-min observation period	Single-dose schedule 0.5 mL intramuscular dose of a *low* egg content vaccine if egg-free vaccine not available in primary care with a 60-min observation period
Higher risk	Previous respiratory or cardiovascular reaction to egg AND positive diagnostics OR 'Lower risk' individual with asthma treated at BTS step 3 or above (long acting β2 agonist in addition to inhaled corticosteroids) [5]	Single-dose schedule 0.5 mL intramuscular dose of a *very low* egg content vaccine if egg-free vaccine not available in hospital with a 60-min observation period	Split dose schedule of a *low* egg content vaccine if egg-free vaccine not available 0.05 mL/0.45 mL intramuscular dose 30 min apart in hospital with a 60-min observation period

OVA, ovalbumin; BTS, British Thoracic Society.

- *Very low* OVA seasonal flu vaccine (<0.12 μg/mL) should be used to immunize egg-allergic individuals if an egg-free vaccine is not available.
- This can be done using a single-dose immunization.
- Patients with lower risk egg allergy should be immunized in primary care. As with all immunization services, facilities should be available and staff trained to recognize and treat anaphylaxis [13].
- All egg-allergic patients immunized with an egg containing vaccine should be observed for 60 min following the procedure as systemic reactions may occur within the hour, but after the standard 20-min routine post-immunization observation period [1, 3].
- Patients with egg anaphylaxis or mild egg allergy and moderate to severe asthma (BTS SIGN step 3 or above) should be immunized using a single-dose protocol, but in a setting used to treating anaphylaxis with a physician in attendance.
- A two-dose split schedule may be required on the discretion of the supervising physician for severe egg allergy, or where a vaccine with *low* OVA content (>0.12 μg/mL but <1.2 μg/mL) is being used.
- Vaccines with unstated OVA content or those >1 μg/mL are not recommended due to lack of safety data.

The expected OVA content of United Kingdom flu vaccines in 2011–2012 is shown in Table 2. Please check the up-to-date Summary of Product Characteristics of the vaccine to ensure appropriate OVA content before vaccine delivery.

Research questions

Despite an increase in knowledge about the safety of influenza vaccines in egg-allergic individuals, several questions of direct clinical importance remain unanswered. First, egg-free vaccines are not licensed for use under 18 years old, despite data suggesting their safety in this age group, and further studies of safety and efficacy may be required [9]. Second, there are limited data on the safety of flu immunization in egg-allergic children who are able to tolerate egg in baked products (such as cake), but not boiled or scrambled egg [3]. Guidelines differ in their approach to these children and an evidence base should establish the risk of immunization in this patient group [1, 14]. It is important to note that OVA in flu vaccine has not been heat treated. Third, the safety of *low* egg vaccines in egg allergy should be explored, especially those with lower OVA content around <0.2 μg/mL.

Table 2. Summary of guidance for the 2011–2012 season in the United Kingdom

Type	Seasonal 2011–2012	Manufacturer	Age indications	Ovalbumin content (μg/mL)	Lower risk egg allergy	Higher risk egg allergy
Egg free	Preflucel	Baxter	From 18 years	No ovalbumin	Single dose in primary care	Single dose in primary Care
Very low egg <0.12 μg/mL	CSL biotherapies generic influenza inactivated influenza	Marketed by Pfizer in UK	From 5 years	<0.04	Single dose in primary care*	Single dose in hospital†
	Enzira	Pfizer	From 5 years	<0.04		
	Inactivated influenza	Sanofi Pasteur MSD	From 6 months	<0.048		
	Intanza 9 μg*	Sanofi Pasteur MSD	From 18 to 59 years	<0.048		
	Intanza 15 μg*	Sanofi Pasteur MSD	From 60 years	<0.048		
Low egg <1.2 μg/mL	Influvac	Abbott	From 6 months	<0.2	Single dose in hospital†	Split dose in hospital†
	Fluarix	GlaxoSmithKline	From 6 months	<0.2		
	Agrippal	Novartis	From 6 months	<0.4		
	Viroflu	Crucell UK	From 6 months	<1.0		
Not appropriate >1.2 μg/mL	Imuvac	Abbott	From 6 months	<2.0	Do not use in egg allergy	Do not use in egg allergy
	Imuvac	MASTA	From 6 months	<2.0		
	Fluvirin	Novartis	From 4 years	<2.0		

Table based on vaccine data from Department of Health [2].

*Note *Intanza* is an intradermal product and the safety of this route of administration has not been established in egg allergy.

†Hospital refers to any healthcare setting used to treating anaphylaxis with a physician in attendance. A single dose is a single injection of the full vaccine dose normally 0.5 mL, a split dose refers to an initial dose of 1/10th, that is, 0.05 mL followed by the remaining 9/10th at an interval of 30 min.

Competing interests

M. E. L. has received reimbursement to attend scientific meetings from GSK and Wyeth and has an unrestricted educational grant for Sanofi Pasteur MSD.

J. L. has no competing interests.

J. O. W. has served on scientific advisory boards, delivered paid lectures and received research grant funds from Danone, Airsonette, Allergy Therapeutics, UCB pharma, Novartis, Merck and Mead Johnson.

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